

Research Article

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Development and Characterization of Controlled Porosity Osmotic Pump Tablets of Captopril

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Abstract

Background: The objective of the present study was to design a porous osmotic pump-based drug delivery system for the controlled release of captopril (Cap) which can maintain a constant therapeutic concentration, thus reducing dose-related side effects and dosing frequency.

Methods: The study evaluated *in vitro* drug release for the controlled porosity osmotic pump tablet (CPOPT) of Cap. This *in vitro* drug release study investigated the influence of the tablet formulation variables such as the amount of mannitol, hydroxypropylmethylcellulose K4M (HPMCK4M), and polyvinyl pyrrolidone (PVP K-30) in the core and the concentration of cellulose acetate and polyethylene glycol 400 (PEG-400) in the coating solution.

Results: It was found that the drug release was mostly affected by the amount of mannitol, HPMCK4M, and PVP K-30 in the core and the amount of cellulose acetate and PEG-400 in the coating solution.

Conclusion: In general, the objective of the study was established by coating the core tablet containing osmotic and pore-forming agents. Therefore, the CPOPT of Cap could be a safe, effective, stable, and promising preparation in the future.

Keywords: Captopril, Osmotic pump, Dissolution, Controlled release drug-delivery system, Swelling polymers

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Background

Oral drug delivery has long been known as the most widely utilized route of administration among all routes that are employed for the delivery of drugs (1). Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages including ease of administration, patient compliance, and flexibility in formulation. However, this approach is limited due to several constraints including the inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract due to variable gastric emptying and motility (2). Prolonged gastric retention improves bioavailability, reduces drug waste, and improves the solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines (3).

Osmotic devices are the most promising strategy-based system for controlled drug delivery. Osmosis is an aristocratic biophenomenon, which is exploited for the development of delivery systems with every desirable property of an ideal controlled drug delivery system. The osmotic system utilizes the principles of osmotic pressure for the delivery of drugs (4). Osmotic devices are the

most reliable controlled drug delivery systems and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a controlled manner. An osmotic pump tablet generally consists of a core containing the drug, an osmotic agent, other excipients, and a semipermeable membrane (SPM) coat (5).

The controlled porosity osmotic pump tablet (CPOP) is a coated tablet with an SPM containing a leachable pore-forming agent (Mannitol). The SPM has no aperture to release the drug, and drug release is achieved through the pores, which are formed in the semipermeable wall *in situ* during the operation. In this system, the drug, after dissolution inside the core, is released from the osmotic pump tablet by hydrostatic pressure and diffusion through pores created by the dissolution of pore formers incorporated in the membrane. The hydrostatic pressure is created either by an osmotic agent or the drug itself after water is imbibed across the SPM (6).

CPOP contains water-soluble additives in the coating membrane, which dissolves after coming in contact with an aqueous environment and results in the formation of a microporous membrane *in situ*. A controlled porosity wall can be described as having a sponge-like appearance (7).

Generally, materials producing from 5 to 95% pores with a pore size of 10A–100 μm can be used in this regard. The resulting membrane is substantially permeable to both water and the dissolved solute. Water-soluble additives used for this purpose are dimethyl sulfone, saccharides, amino acids, and sorbitol (8).

Captopril (Cap) was chosen as one of the angiotensin-converting enzyme inhibitors, which is a widely used and effective drug for the clinical treatment of different kinds of high blood pressure diseases (9). It has been reported, however, that the duration of the antihypertensive action after a single oral dose of Cap is only 6-8 hours, thus the clinical use requires a daily dose of 37.5-75 mg to be taken three times (10). Although Cap is rapidly absorbed through gastrointestinal tract, its bioavailability decreases by 30%-40% in the presence of food. The half-life of Cap is less than 3 hours. The objective of the present study was to design Cap CPOPT, which can maintain a constant therapeutic concentration, thus reducing dose-related side effects and dosing frequency.

Materials and Methods

Materials

Chemicals

Cap was supplied by Wockhardt Pharmaceutical Ltd. Aurangabad (India). In addition, Di-calcium phosphate (Mannitol) and HPMCK4M were obtained from S.D. Fine-Chem Ltd. Mumbai (India) and Colorcon Asia Pvt. Limited Goa (India), respectively. Further, PVP K-30 and cellulose acetate (PEG-400) were supplied by BASF Limited, Mumbai (India) and Thomas Baker Pvt. Ltd. Mumbai (India), respectively. Acetone, Methanol was supplied by Merck (India). All other applied reagents were of either high-performance liquid chromatography or analytical grade.

Methods

Preparation of Core Tablets

The core tablets of Cap were prepared by the wet granulation method and the batch size was kept as 200 tablets. The basic composition of the tablet core and all

excipients are listed in Table 1.

All ingredients were weighed accurately, blended homogeneously, and passed through a 60 # mesh sieve except for lubricants. The mixture was then granulated with a (10% w/v) starch paste and the resulting wet mass was passed through an 18-mesh sieve. The granules were dried at 50°C for 30 minutes in a hot air oven. Finally, the dried granules were blended with magnesium stearate and talc for 10 minutes in a polybag and were compressed into tablets with an average weight of 30 mg) using a single stroke tablet punching machine (Cadmach, India) fitted with a 9 mm round concave punch. The core compression was maintained at the range of 85-105 MPa during the compression of core tablets (11). The average hardness of the compressed tablets was found to be $6.28 \pm 0.32 \text{ kg/cm}^2$ while the average thickness was found to be $4.15 \pm 0.152 \text{ mm}$.

Coating of Core Tablets

The three coating solutions of cellulose acetate in a mixture of acetone and methanol containing different levels of a pore-forming agent, namely, PEG-400 (10% w/v, 15% w/v, and 20% w/v) were prepared for SPM coating. Table 2 presents the compositions of the coating solution used for coating the tablets.

The core tablets of Cap were coated with cellulose acetate in an automated perforated pan (Ganscoater, India). Various components of the coating solution were added to the solvent mixture in a sequential manner. The sunset

Table 2. Coating Solution Composition of Captopril Osmotic Pump Tablet Compositions in Terms of % W/W

Ingredient	Coating Code		
	A	B	C
Cellulose acetate	3	3.6	4.2
PEG-400	0.3 (10%)	0.45 (15%)	0.6 (20%)
Acetone (mL)	90	90	90
Methanol (mL)	10	10	10

Note. PEG-400: Polyethylene glycol 400; Total solids in the coating compositions: 4.0%.

Table 1. Composition of the Osmotic Pump Tablets of Captopril Containing Osmogent Along With a Solubility Modifier Polymer

Ingredient (mg)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Captopril	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
HPMCK4M	10	20	30	-	-	-	-	-	-
PVP K-30	-	-	-	10	20	30	-	-	-
Mannitol	140	140	140	140	140	140	140	160	180
Di calcium phosphate	108.5	98.5	88.5	108.5	98.5	88.5	118.5	98.5	78.5
Starch paste 10%w/v	QS	QS	QS	QS	QS	QS	QS	QS	QS
Talc	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2

Note. HPMCK4M: HydroxypropylmethylcelluloseK4M; PVP K-30: Polyvinyl pyrrolidone; QS: quantum sufficit.

lake color was added to the coating solution. First, the added component was allowed to dissolve before adding the next component. The coating was carried out by a pan coater. The rotating speed of the pan was kept at 20 rpm. The coating solution was sprayed using a spray gun with a nozzle diameter of 1 mm at a spray rate of 3-5 mL/min. The atomization pressure was kept at 1 kg/cm² while the outlet temperature was kept at 45°C. The coating was continued until desired weight gain (12%) was obtained on core tablets. In all cases, the coated tablets were dried at 50°C for 10 hours before further evaluations (12).

Drug Content Determination

The Cap core tablets were tested for their drug content. Five tablets were powdered finely. The quantity of the powder equivalent to 50 mg of Cap was accurately weighed and transferred to a 100 mL of a volumetric flask. The flask was filled with the simulated intestinal fluid (SIF) buffer solution at a pH of 6.8 and mixed thoroughly. The solution was made up to the volume and filtered as well. From the resulting solution, 10 mL was taken, diluted to 100 mL with the same SIF (pH of 6.8), and the absorbance was measured at 202 nm using a Shimadzu UV-visible spectrophotometer (13).

In Vitro Dissolution Studies

The developed formulations of Cap were subjected to *in vitro* dissolution studies using a USP-Type II dissolution apparatus (Electrolab, India). The rotation speed of the paddle was kept at 50 rpm, and the temperature was maintained at 37±0.5°C. The dissolution study was carried out in 900 mL of two different dissolution media (i.e., the first 2 hours in 0.1 HCl, followed by a SIF of a pH of 6.8 for subsequent hours). At regular time intervals, 10 mL samples were withdrawn and replaced with an equivalent amount of a fresh medium to maintain sink conditions. The withdrawn samples were filtered and then analyzed at 202 nm and 217 nm for the first 2 hours, and the next 10 h using a UV-Visible spectrophotometer, respectively (14).

Surface Membrane Morphology

The obtained coating tablets before and after the dissolution test were examined for their surface membrane morphology by an electron microscope. The membranes were dried at 45°C for 12 hours and stored between the sheets of wax paper in a desiccator before the examination. The membrane samples were sputter-coated for 5-10 minutes with gold by using a fine coat ion sputter and then examined under electron microscopy (15).

Curve Fitting Analysis

The mechanism of Cap release from the osmotic pump tablets is controlled by various factors such as osmotic pressure, coating thickness, the permeability of the membrane, the solubility of the pore-forming agent, and the like. Release kinetics were determined by fitting the

dissolution data of the F1A, F1B, and F1C batches in the following models of the zero order, the first order, the Higuchi model, and the Korsmeyer-Peppas model. Finally, the mechanism of drug release was decided based on the R² values that were obtained from software models (16).

Stability Studies

To assess the stability of the drug and formulation, the optimized formulation of Cap (F1B) was packed in the strips of 0.04 mm thick aluminum foil laminated with polyvinyl chloride by strip packing and was stored in the International Conference on Harmonisation (ICH) certified stability chambers (Thermo labs, Mumbai) maintained at 40 °C and 75% relative humidity for 3 months (zone III conditions as per ICH Q₁ guidelines). The samples were withdrawn periodically and evaluated for their hardness, friability, content uniformity, and *in vitro* drug release (17).

Results and Discussion

Effect of the Formulation Aspects of Core Tablets

Effect of the Swelling Polymer on an In Vitro Drug Release Study

HPMCK4M and PVP K-30 are hydrophilic materials. Changes in their concentrations in the formulation lead to a change in drug release. The *in vitro* release profiles of formulation F1B to F6B containing different amounts of swelling polymers of HPMCK4M and PVP K-30 (Figure 1), indicating the effect of HPMCK4M and PVP K-30 on the release rate. The release rate was found to decrease by an increase in the concentration of HPMCK4M and PVP K-30. This is because the swelling rate and viscosity due to higher internal pressure in the core increases by an increase in HPMCK4M and PVP K-30 so that the water entry into the core is hindered resulting in a decreased rate

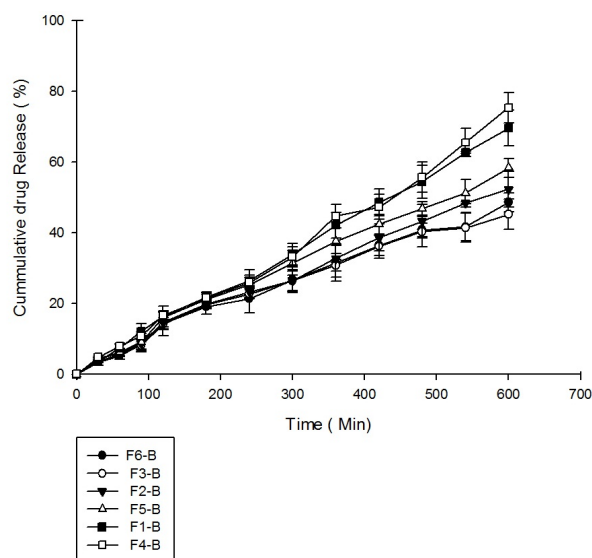


Figure 1. *In Vitro* Release Studies of the Captopril of Batches F1B, F2B, F3B, F4B, F5B, and F6B.

of drug release.

Based on the data in Figure 1, all formulations containing different amount of polymers showed different drug release patterns. PVP K-30 showed higher drug release compared to HPMCK4M. The formulations F1B, F2B, F3B, F4B, F5B, and F6B demonstrated 73.48%, 62.47%, 48.46%, 78.89%, 66.37%, and 53.72% drug release in 10 hours, respectively. The batch F1B represented 73.48% of drug release in 10 hours, hence, it was considered as the optimized formulation.

Effect of the Osmotic Agent on an In Vitro Drug Release Study

The CPOPTs of Cap were prepared with different amounts of mannitol as an osmotic pressure agent in the core. The results are shown in Figure 2.

A significant influence was observed in this regard. The release rate accelerated by an increase in the amount of mannitol because the increasing osmotic pressure made more drug release from the core. When the coated tablet was exposed to aqueous environment water diffused through the membrane, hydrating the core. The salvation of osmotic agents creates an osmotic pressure difference between the core contents and the external environment, which resulted in greater Cap release. The F7B, F8B, and F9B formulations containing different numbers of osmotic agents showed 80.47%, 89.23%, and 95.36% drug release in 10 hours, respectively.

Effect of Membrane Variables

Effect of the Pore Forming Agent on an In Vitro Drug Release Study

The amount of PEG-400 (pore former) in the coating formulation was verified and its effect on the drug release of three formulations was evaluated as well. For this purpose, PEG-400 concentrations 10, 15, and 20% w/w of PEG-400 were utilized for coating the optimized core formulation (F1). Formulations F1A, F1B, and F1C containing 10%, 15%, and 20% of PEG-400 released 69.23%, 78.89% and 89.43% of Cap in 10 hours, respectively (Figure 3). Formulation F1C indicated high drug release possibly due to high concentrations of PEG-400.

Based on the obtained data (Figure 3), the release rate of Cap increased by an increase in the amount of PEG-400. As the percentage of PEG-400 increased, the membrane became more porous (in contact with the aqueous environment) due to the solubilization of the water-soluble PEG-400 in dissolution media resulting in faster drug release. Drug release from controlled porosity osmotic systems takes place through pores formed *in situ*. A microporous membrane coating appears to be the key factor with respect to release kinetics.

Effect of the Weight Gains of the Semipermeable Membrane on an In Vitro Drug Release

To study the effect of the weight gain of coating on drug

release, the optimized formulation F1B with different weight gains (i.e., 10, 12, and 14% w/w, respectively) of the microporous membrane was prepared to demonstrate the effect of coating thickness on drug release. Figure 4 displays the release profile of Cap from these formulations showing the effect of the weight gain on drug release.

The results indicate a decrease in drug release with an increase in the weight gain of the membrane. The decrease in drug release can be due to an increase in the thickness of the coat causing poor penetrations of the fluid into the core, hence, less solubilization of the drug and poor release. No bursting of the systems was observed during the dissolution run in any of the formulations.

Surface Membrane Morphology

To study the changes in the membrane structure throughout the dissolution procedure and the mechanism

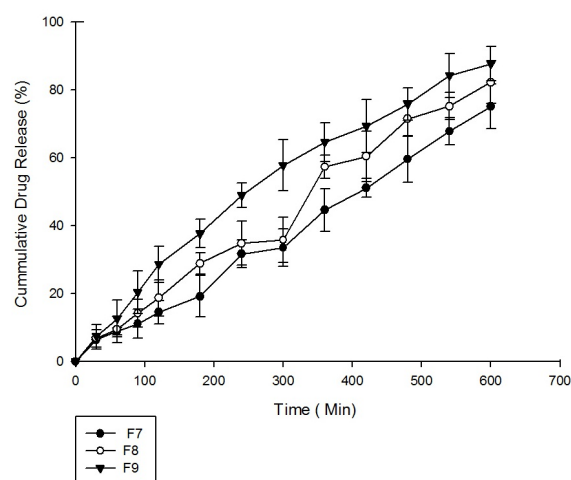


Figure 2. *In Vitro* Release Profiles Showing the Effect of the Concentration of the Osmotic Agent on Captopril Release.

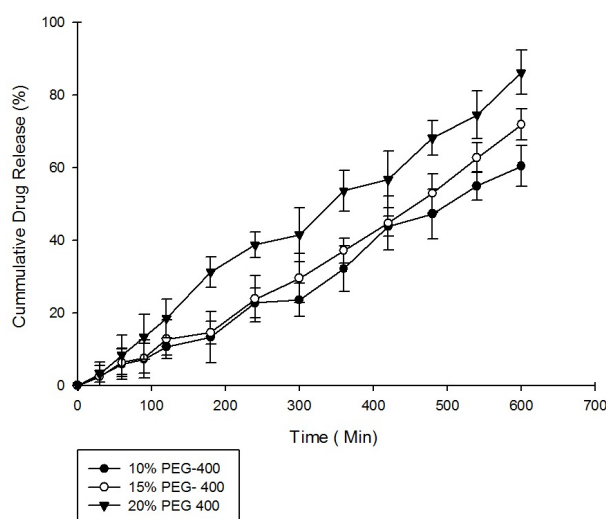


Figure 3. Effect of the Concentration of the Pore-forming Agent on Captopril Release.

of drug release from the CPOPTs of Cap, formulations obtained before and after complete dissolution were subjected to scanning electron microscopy (SEM) studies. Before dissolution studies, no porous membrane structure was observed with the presence of different levels of the pore former (PEG-400). The surfaces of the coated tablets were glossy and the membrane appeared to be integral and smooth with no visible imperfections. Figure 5a shows the SEM micrographs of the surface of membranes after simulated gastric fluid dissolution studies, suggesting that there was no evidence of pore formation in the membrane in all formulations.

Pores in the membranes were observed after exposure to SIF (Figure 5b) which possibly acted as an exit for the drug released. Based on the comparison between formulations F1A, F1B, and F1C, containing 10% w/w, 15% w/w, and 20% w/w of the pore-forming agent (PEG-400), the formulation F1A showed the least pore size and formulation F1C became more porous and cause the rupturing of the membrane during dissolution. Thus, the SEM study suggested that 15% w/w of PEG-400 can be considered as the optimum concentration for obtaining the maximum release rate without causing the rupturing

of the membrane.

Curve Fitting Analysis

The release profiles of Cap containing formulations F1A, F1B, and F1C were processed into the table to compare different orders of drug release and to understand the linear relationship (i.e., kinetic principles).

The linear nature of plots between percent cumulative drug release and time suggested that none of the formulations follow first-order release kinetics. This is further confirmed by the very high value of the sum of squared residuals and comparatively less volumes of the correlation coefficient (r). Moreover, the Higuchi model showed high simple sequence repeat values and less correlation coefficient volumes as compared to zero-order release kinetics for all formulations (Table 3).

The drug release data were further analyzed for curve-fitting analysis based on the Korsmeyer-Peppas model and the results (Table 3) confirmed that all formulations showed non-Fickian diffusion kinetics ($n > 0.5$).

Stability Studies

The accelerated stability studies were carried out according to ICH guidelines. After a period of 3 months, the samples were observed for any change on the coating membrane. The optimized formulation F1B was found to be stable in

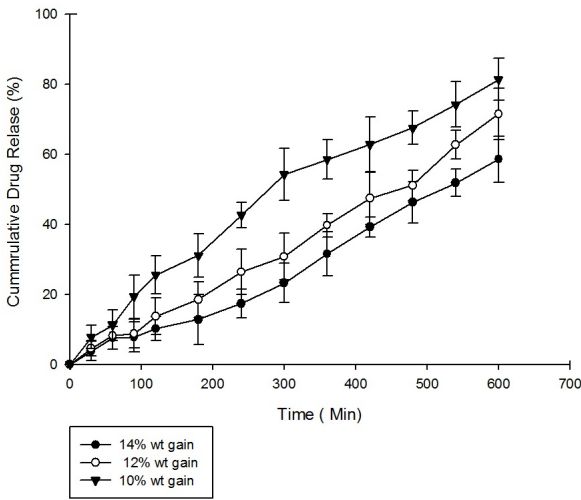


Figure 4. Effect of Membrane Weight Gain on the Captopril Release of F1B Formulation.

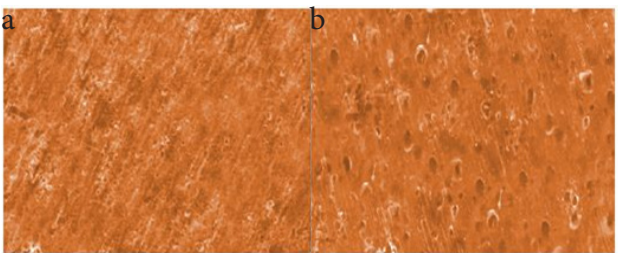


Figure 5. Scanning Electron Photomicrographs of Tablet (a) Obtained Before Dissolution and (b) Porous Region of Membrane Containing 10% w/w PEG-400. Note. PEG-400: Polyethylene glycol 400.

Table 3. Statistical Analysis and Correlation Coefficient Values for the Dissolution Data of Different Formulations Based on Kinetic Models

Kinetic Models	Parameters	Formulation		
		F1A	F1B	F1C
Zero order	R ²	0.9867	0.9929	0.9937
	R	0.9933	0.9964	0.9968
	SSR	56.7821	35.5052	45.5052
	Intercept	4.4828	1.9076	1.4729
	K ₀	8.7842	7.6078	6.3984
First order	R ²	0.9703	0.9173	0.9634
	R	-0.9850	-0.9577	-0.9815
	SSR	142.721	154.842	151.391
	Intercept	2.0484	2.0535	2.0306
	K ₁	-0.0836	-0.0583	-0.0423
Higuchi model	R ²	0.9625	0.9008	0.8986
	R	0.9811	0.9491	0.9479
	SSR	193.4283	205.3261	214.2973
	Intercept	10.59	16.214	13.4405
	k _H	7.656	25.3946	21.3231
Korsmeyer-Peppas model	R ²	0.9966	0.9943	0.9867
	R	0.9984	0.9971	0.9925
	SSR	0.004901	0.0126	0.0246
	Intercept	1.0877	0.7930	0.7858
	N	0.8803	0.8809	0.7861

Note. SSR: Simple sequence repeat.

Table 4. Stability Studies Data of Optimized Batch F1B Formulation After Three Months of Storage Conditions at 40 °C and 75% RH

Parameter	Initial	Three Months
Drug content (% $\pm$ SD)	99.51 $\pm$ 2.44	100.32 $\pm$ 1.16
Hardness (kg/cm ² $\pm$ SD)	7.23 $\pm$ 0.20	8.02 $\pm$ 0.53
Friability	0.0506	0.0621
MDT 50% (h)	7.12 hours	7.65 hours

Note. RH: Relative humidity; SD: Standard deviation; MDT: Mean dissolution time.

terms of drug content, and a slight increase was observed in hardness and friability while the *in vitro* release profile was as shown in Table 4.

The *in vitro* release profiles of F1B formulation initially and after 3 months were nearly comparable, and a negligible difference was observed, thus the developed formulation was found to be stable for the given storage conditions.

Conclusion

The present study was carried out to develop the CPOPT of Cap that could maintain a constant therapeutic concentration, thus reducing dose-related side effects and dosing frequency. The objective was established by coating the core tablet containing osmotic and pore-forming agents. Based on the *in vitro* study results, the tablets maintained their integrity throughout the release. SEM studies confirmed the formation of pores in the membrane after coming into contact with the aqueous environment. The curve fitting analysis of release data proved that the system could provide the required controlled release rate of the drug. Pharmacokinetic research indicated that the CPOPT of Cap could prolong the effective drug duration while reducing the frequency of taking the drug and lowering the max blood concentration of the drug, which could greatly reduce dose-related side effects. Therefore, the CPOPT of Cap could be a safe, effective, and stable and promising preparation method in the future.

Conflict of Interests

The authors report no conflict of interests.

Acknowledgements

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